UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	:	**March 27, 2007**
LISZIEWICZ, et al.	:	**Atty Docket No. RGT 9771**
Serial No. 10/081,922	:	**Group 1632**
Filed: 21 Feb 2002	:	**Examiner: Wilson**

For: Method of Delivering Genes into Antigen Presenting Cells of the Skin

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Mail Stop Appeal Brief, Patents
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Response to Notification of Non-Compliant Appeal Brief [1]

In response to a Notification of Non-Compliant Appeal Brief bearing a mail date of March 13, 2007, enclosed are pages 7- 52 of the Appeal Brief. Per conversation with the Examiner, the Brief has been amended to include a separate section titled Grounds of Rejection to be Reviewed on Appeal, and to summarize the 46-page Final Rejection. The Examiner's recommendation to delete all the references to the specification by page and line number in the Summary of Claimed Subject Matter, must be declined in light of 37 CFR 41.37 (c)(1) (v) and item 5 of the Notice, as well as the assertions in the Final Rejection that this application lacks support for the Claims. Similarly, the suggestion to delete copies of evidence entered by the examiner and relied upon by appellant in the appeal must also be declined in light of 37 CFR 41.37 (c)(1)(ix), and item 8 of the Notice.

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[1] This paper is being forwarded by Fax to the Commissioner of Patents, P.O. Box 1450 Alexandria, VA 22313-1450 on March 27, 2007. Signed Valerie E. Looper Valerie E. Looper

CFC received 26 pages

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1. New Matter – Claim 23

Whether the phrase "one or more compounds selected from the group consisting of sugars, polyethylenimine, and polyethylenimine derivatives" in claim 23 is objectionable under 35 USC § 112 as new matter.

2. Written Description

A. Claims 23-26, 28, 35 and 37-39 - "one or more compounds"

Whether the phrase "one or more compounds selected from the group consisting of sugars, polyethylenimine, and polyethylenimine derivatives" in claim 23 is objectionable under 35 USC § 112 as lacking written description, even though the language in the application is admittedly supported.

B. Claims 37-39 Therapeutic Effect/Correlation of Experiments

Whether the claimed method fails to meet the written description requirement of 35 USC § 112, where the language is found in the application text, where a known therapeutic effect is demonstrated in vitro and in vivo in the application text, is supported by Declaration and peer-reviewed publication, and the claimed invention is the subject of human clinical trials.

3. Enablement – Claims 37-39

Whether the claimed method is objectionable as being not enabled under 35 USC § 112, where the claimed method is admittedly described, where a therapeutic result is demonstrated in vitro and in vivo, and where the claimed method is further supported by Declaration and peer-reviewed publications by the inventors, and is the subject of human clinical trials.

4. Indefiniteness – Claims 23, 30 and 31

Whether the claimed method is objectionable as being indefinite under 35 USC § 112, for various reasons. Claim 23 is said not to have a preamble agreeing with the body of the claim, whether the terms "transfecting" "applying" and "gene delivery complex that targets antigen presenting cells" are indefinite.

Whether Claim 30 is indefinite because it is a dependent claim that does not relate to every material listed in the independent Claim.

Whether Claim 31 is indefinite because the phrase "is formulated in a glucose solution" is unclear.

5. Anticipation – Claims 23-26, 28, 30-32, 37, 40, 41 and 43

Whether Claims 23-26, 28, 30-32, 35, 37, 40 41 and 43 are properly rejected under 35 U.S.C. 102(e) as being anticipated by Behr (US Patent 6,013,240) as supported by Carson (US Patent 5,679,647)

6. Obviousness – Claims 23-26, 28, 30-32, 37, 40, 41 and 43

Whether Claims 23-26, 28, 30-32, 35, 37-41 and 43 are properly rejected under 35 U.S.C. 103(a) as being unpatentable over Behr (US Patent 6,013,240) as supported by Carson (US Patent 5,679,647) and in view of Holler (US Patent 5,908,923).

7. Request for Relief

Whether the applicant, in addition to issuance of the Claims, is entitled to further relief in the form of a term extension.

ARGUMENTS

1. New Matter

The Applicants cannot tell whether the present objection with respect to new matter has been withdrawn. While the Examiner has clearly and courteously stated that he was seeking support from the text of the present application, the applicants are aware that a "new matter" objection is an objection that the specification of present application does not conform to the specification of the parent. The present question involves an objection to language in a claim, not an amendment to the abstract, specification, or drawings in the application. Under the published practice of the United States Patent and Trademark Office, claim language is not properly rejectable as new matter (MPEP 2163.01; MPEP 2163.06, In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981).

This limitation is supported by the text of the present application at least at page 15, lines 6-8 and 16-17, as well as at example 10 and Table 2, where DNA, PEI, and modified PEI were all formulated in 8% glucose, and that for the transcutaneous method, DNA formulated with sugar only was the most efficient gene delivery system.

This same information can be found in the parent patent, USPN 6,420,176 (Evidence – 1). It is undisputed that this patent discloses the use of DNA in combination with PEI, PEI modified with various sugars, including mannose, galactose and glucose (in saline solution, Experiment 6, Col. 14, line 63, Table-1), and DNA alone, DNA in combination with PEI and PEI modified with mannose (formulated in glucose solution, Experiment 8, Col. 15, final line, Table 2) and the surprising results for cutaneous delivery for DNA complexed with glucose alone is discussed (Example 10). Applicants submit that the claim language cannot reasonably be construed as new matter.

There is no new matter in this case. The text of the parent and present applications are identical.

2. Written Description.

A. Claims 23-26, 28, 35 and 37-39 - "one or more compounds"

The limitation of "one or more compounds selected from the group consisting of sugars, polyethylenimine, and polyethylenimine derivatives" in claim 23 is said to lack written description because not enough different combinations of the members of the group are demonstrated. This application discloses the use of DNA in combination with PEI, PEI modified with various sugars, including mannose, galactose and glucose (in saline solution, Experiment 6 at page 21 line 15, Table 1), and DNA alone, DNA in combination with PEI, and DNA in combination with PEI modified with mannose, each combined with a sugar (formulated in glucose solution, Experiment 8, page 22, line 35 , Table 2) *in the experiments.* Applicants submit that this is sufficient support for the claimed language "DNA one or more compounds selected from the group consisting of sugars, polyethylenimine, and polyethylenimine derivatives."

B. Claims 37-39 Therapeutic Effect/Correlation of Experiments

Claims 37-39 remain rejected under written description even though the specification is admitted to describe an immune response in an animal, because the Examiner says the immune response that is obtained may not be capable of treating or preventing HIV. It is noted that Claims 23-26, 28, 30-33, 35 and 40-43 are not subject to this rejection. The specification is admitted to describe using the method claimed to induce an immune response in an animal; it is admitted that claimed materials were described, and that transfection has been demonstrated; and it is also admitted that the claims do not require inducing an immune response or treating or preventing HIV.

Thus the question is whether the examiner's requirement for a further demonstration of a therapeutic response is appropriate, and if appropriate, whether this additional burden has been met by the text of the application, and in addition, by copious, peer-reviewed data submitted by the applicant, and the approval of this vaccine by the FDA for clinical trial.

The written description requirement relates to whether the claimed subject matter was described in the application (MPEP 2163). A description as filed is presumed to be adequate (MPEP 2163.04). The burden on the Examiner is found in MPEP 2163.04 I:

(A) Identify the Claim Limitation at issue.

(B) Establish a prima facie case by providing reasons why a person skilled in the art at the time the application was filed would not have recognized that the inventor was in possession of the invention as claimed in view of the disclosure of the application as filed. A general allegation of "unpredictability in the art" is not a sufficient reason to support a rejection for lack of adequate written description.

upon reply, MPEP 2163.04 II states that the Examiner has specific responsibility:

Upon reply by applicant, before repeating any rejection under 35 U.S.C. 112, para. 1, for lack of written description, review the basis for the rejection in view of the record as a whole, including amendments, arguments, and any evidence submitted by applicant. If the whole record now demonstrates that the written description requirement is satisfied, *do not repeat the rejection in the next Office action.* (emphasis added)

The text and the experimental results submitted by the applicants are entitled to a reasonable amount of credit: MPEP 707.07(l) provides:

> The results of the tests and examples should not normally be questioned by the examiner unless there is reasonable basis for questioning the results. If the examiner questions the results.... The applicant must reply to the rejection, for example, by providing the results of an actual test or example which has been conducted, or by providing relevant arguments that there is strong reason to believe that the result would be as predicted.

In the present case, criterion A is not met, because there is no claim limitation in issue. The Claims are directed to a method of transfecting cells, and that method has been demonstrated. The Examiner has admitted the claimed method has been described, and that the various materials used in the method and mentioned in the application have been used to transfect cells and raise an immune response in examples in the application. The Examiner has objected however, that the art was and is unpredictable, that the examples don't correlate with the claimed invention, and that neither the inventors' proffer of affidavits, nor peer-reviewed

articles supporting the statements in the application, nor notice of a decision by the FDA to allow clinical trial of the claimed invention is sufficient to overcome his objections.

The Claimed invention is:

A method of transfecting antigen presenting cells, the steps comprising

selecting a gene delivery complex that targets antigen presenting cells, comprising DNA and one or more compounds selected from the group consisting of sugars, polyethylenimine, and polyethylenimine derivatives,

and applying the complex to the skin or mucosa surfaces of an animal,

wherein said DNA comprises a nucleic acid sequence encoding at least one immunogenic protein operatively linked to a promoter. This method is acknowledged to find support in the application. The question raised by the Examiner is whether the specification supports the further limitations, wherein the protein is from a human immunodeficiency virus (Claim 37); that is replication-defective (38); by virtue of being integration-defective.

1. The Claim Language was approved in the Parent Application.

It is further noted that the present application is a division of USPN 6,420,176, re: Composition for Delivering DNA into Antigen Presenting Cells, which has the same specification as the present application, and includes the following dependent Claims (copy enclosed at Evidence Appendix – 1):

> 3. The gene delivery complex of Claim 2, wherein the reverse transcriptase-dependent virus is *a human immunodeficiency virus.*
> 4. The gene delivery complex of Claim 3, wherein the human immunodeficiency virus is *replication-defective.*
> 5. The gene delivery complex of claim 3, wherein the human immunodeficiency virus is *integration-defective.*

In an effort to expedite prosecution, the limitations with respect to the material used in the present claimed method were made to quote those of the parent patent. Similar limitations are also found in the parent patent, at Claims 11-13. The Applicants note that the issues involving written description and enablement were raised by the Examiner during prosecution of the parent patent and resolved at that time. The Applicants have a right to uniform application of the patentability standard (MPEP 706 I; MPEP 707.07(j)). Piecemeal Examination is to be

avoided (MPEP 707.07(g)). Inventions relating to HIV/AIDS and cancer are specifically important, and suitable for expedited processing. (MPEP 708.02 X.) And, applications that are substantially allowable should be considered special and prompt action taken to require correction of formal matters (MPEP 1301). Even in ordinary cases, the Examiner should never overlook the importance of his or her role in allowing claims which properly define the invention (MPEP 706). The examiner's action should be constructive in nature and when possible should offer a definite suggestion for correction (MPEP 706 II).

The Examiner has admitted that the claimed method meets the written description requirements, and the objections with respect to written description relate back to language that was considered and allowed in the parent patent.

2. The Claimed Material was used in an Experiment in the Application, and produced a Therapeutic Result, which has been confirmed by Subsequent, Peer-Reviewed Publication.

The claimed function of the method is to transfect antigen presenting cells. The Examiner has acknowledged that transfection of antigen presenting cells has been demonstrated, and has acknowledged that a CTL response was obtained.

The Examiner has made a requirement for a further showing of a therapeutic or prophylactic effect using a subset of materials. The Applicants have pointed to Example 4, page 20, which discloses that an immune response, that is, a CTL response, had been obtained in at least one animal after a single immunization attempt, using a LW/Int- plasmid (disclosed at page 18, lines 30-31 as a plasmid DNA encoding an integration and replication defective HIV). That immune response is evidence that the claimed effect, transfection of antigen presenting cells, has been achieved, and further that the stated purpose of transfection using the described embodiment, to raise an immune (CTL) response, has been achieved.

The application discloses that CTL responses are associated with therapeutic effects at page 4, lines 7-11: "Expression of foreign genes in antigen presenting cells (APC) may be used to generate efficient CTL response in animals. Therefore, gene transfer and genetic modification of APC has the potential to generate effective vaccine and therapeutic approaches ...." That is, generation of a CTL response is a legitimate marker for a therapeutic effect.

The Examiner states that Example 4 does not correlate with the claimed invention, however, because Example 4 does not use the claimed method of delivery of genes through the

skin. However, the Applicants point out that Example 4 was included to show efficacy of the claimed materials in a more classical method, such as described in USSN 08/803,484 (incorporated by reference and enclosed at Evidence Appendix – 2). The application discloses in the discussion at the end of Example 9 that

> These experiments show that PEI-(Man)-DNA complexes are able to penetrate in the skin, and deliver the DNA into Langerhans cells. The Langerhans cells were activated and migrated into the draining LN and expressed genes encoded by the DNA construct in the LN. It is known that cultured DC reinjected to the body migrate in the LN and generate efficient immune response. This invention demonstrates that in vitro isolation of DC is not required to transfer genes into Langerhans cells, or for gene expression in the lymphoid organs. We have also demonstrated that expression of a replication defective virus in DC results in efficient induction of a CTL response in vitro and in vivo (see above *sic*: This is a reference to Example 4). Therefore, we have shown that transcutaneous gene delivery with complexes (like PEI-man-DNA) can be utilized to generate immune responses against proteins encoded in the DNA.

Further, the Applicants have submitted an article by the inventors from a peer-reviewed journal, Lisziewicz, et al., "DermaVir: A Novel Topical Vaccine for HIV/Aids" J Invest Dermatol, 2004 detailing the use of the present invention to produce CTL responses (Enclosed at Evidence Appendix 4). That article begins as follows:

> "One strategy for a new immunotherapeutic intervention against human immunodeficiency virus (HIV) infection is to develop a vaccine that can reconstitute HIV-specific immunity, thereby improving the efficacy of the present antiretroviral regimens. The therapeutic efficacy of such a vaccine would be mediated by HIV-specific T cells...."

This article is consistent with the teachings of the present application, and its acceptance for publication is some evidence that others of skill in the relevant art agree with the inventors that the CTL response is an acceptable marker for a therapeutic response. This article also includes a detailed discussion of a comparison between the immune responses raised via topical immunization and *ex vivo* immunization. The entire discussion revolves around T cell responses. See page 6, Col. 1. The authors conclude at page 7, first full paragraph, lines 1-3 that "We have shown here in a primate model that topical DermaVir vaccination is comparable with *ex vivo* DC-based vaccination." This article confirms the results disclosed in the present application, and is some evidence that those of skill in the art accept the results shown in the present application.

Yet another article consistent with the teachings of this application is Lori (Current Medical and Chemical Anti-infective Agents, 2004, Vol. 3, pg 31-41) (Evidence Appendix 7), which discusses the present invention, which has been shown to be of value as a treatment for existing viral infection. This reference has been cited by the Examiner as teaching that an HIV-specific immune response in vivo against HIV protein fails to provide a therapeutic or prophylactic effect (pg 31, col.1, 2nd ¶, lines 7-10), and the Examiner claims that this result must necessarily be extended to the present invention. This reference demonstrates the failure of others. The passage cited by the Examiner states in full:

> "The desired phenotypical endpoint of this clinical trial was the production of protective neutralizing **antibodies**. Unfortunately, the analysis of the date from this trial did not indicate a significant reduction in overall infection rates based on the production of protective HIV specific **antibodies**." (emphasis added)

What the reference says about the present invention is "our DC targeted HIV vaccine, DermaVir, a topical, therapeutic vaccine that has demonstrated immunological and clinical benefits in rhesus macaques" at page 32, Column 1, 1st full para, lines 1-5 up. The article, at pages 38-39, describes the vaccine as "(i) plasmid DNA, encoding a full-length replication and integration defective HIV, (ii) plyethylenimine-mannose (PEIm), a chemical polymer and (iii) glucose solution," (p. 38, col. 2, 1st full para.) presents pre-clinical studies, page 38-39, a theoretical basis to explain why the vaccine differs from other vaccines and its advantages over others (page 39, 2nd and 3rd full para.) and a suggestion for its treatment as a new antiretroviral approach complementary to that of various drug classes (page 39, paragraph bridging Cols 1 and 2).

Example 4 demonstrates the efficacy of the claimed materials in the *ex vivo* method; the other examples demonstrate that the topical method works as well as or better than, the *ex vivo* method for very similar materials, except that a marker gene is used, the discussion in the disclosure ties the two materials together, and the subsequent publications demonstrate that the disclosure in the application is acceptable for publication in peer-reviewed journals.

3. The Experiments overcome the State of the Art because the predicted results are demonstrated.

The Examiner has cited a number of articles, some of which pre-date, and some of which post-date, the file date of the present application. According to the Examiner, these articles establish that state of the art prior to the making of the claimed invention was that the likelihood of inducing an immune response "capable of treating retroviral infection" was unpredictable.

While the Examiner may use whatever relevant information is at hand to establish a prima facie case questioning statements in an application, such prima facie case is overcome when the applicant can point to either text in the application, new experimental results, or argument showing that there is a strong reason to believe that the results will be as predicted. MPEP 707.07(l). In this case, the predicted results are transfection of antigen presenting cells, and the disclosed purpose for the present embodiment is to raise an immune response. The applicants have admittedly pointed to experimental results that produce the predicted result: transfection of antigen presenting cells, as shown by the raising of an immune response.

The Examiner admits that the specification describes the use of LW/int- plasmid encoding replication-defective, integrase-defective retroviral DNA in the claimed invention; and that replication-defective, integrase-defective retroviral DNA was described in related application 08/803,484); that Example 4 teaches transfecting dendritic cells in vitro with the LW/Int- plasmid and injecting the dendritic cells into monkeys (split subcutaneously and intravenously); that one monkey showed a CTL response (pg 20, lines 8-19); that Example 9 teaches applying a gene delivery complex encoding GFP to th [sic: presumed to be "the skin"] of mice, and that GFP protein was expressed in dendritic cells.

Because the Examiner has admitted that the text of the application describes the use of the claimed materials in the claimed invention, and acknowledges the proffered experiments yield the predicted results (transfection of cells; immune response) the Examiner has admitted that the invention is described in the application.

To the extent that the Examiner has questioned whether the admittedly described invention will actually enable anyone to treat a specific disease, his arguments are more properly related to the enablement requirement. The Examiner has repeated these arguments in an enablement rejection that is discussed below.

3. Enablement – Claims 37-39

Although the method described in Claims 37-39 is admittedly enabled, the Claims remain rejected because, it is said, the cells transfected according to the method may not induce a therapeutic or prophylactic immune response. Claims 23-26, 28, 30-33, 35 and 40-43 are admittedly enabled. This is essentially the same rejection as the Written Description rejection above, and many of the same arguments apply. For the sake of brevity and clarity, the argument with respect to written description above has been limited to the extent possible to the underlying facts. That is, to a discussion of the Written Description requirement in terms of what is in the disclosure. With respect to enablement, the focus shifts to the showing that the disclosure is credible, that is, whether the Claims are supported by experimental results, and whether the teachings of the application have been confirmed by subsequent work of both the authors and others.

A. Applicable law: 35 USC § 101 and § 112 – Utility, Enablement, Written Description

The Examiner has stated that the Applicants have not cited applicable or controlling law. The Examiner attempts to avoid the applicable precedent by characterizing the present rejection as relating to "utility and not enablement." Upon further review, the applicants note that the statement of law previously supplied is correct. The controlling case law remains *In re Brana*, 51 F.3d 1560, 34 USPQ 2d 1436 (Fed. Cir. 1995), where the Federal Circuit reversed a decision by the United States Patent and Trademark Office (PTO) Board of Patent Appeals and Interferences (Board) affirming an Examiner's rejections of claims to antitumor compounds for failure to comply with 35 USC §112, 1st ¶.

In re Brana was decided in 1995. At the time the Federal Circuit observed that the question of what an applicant must prove with respect to the utility of pharmaceutical preparations had been settled by the case law, citing cases in its predecessor court that went back to 1961 (*id* at 51 F.3d 1560, 1564). The Court also noted that the utility requirement is found in 35 USC § 101, but that the requirement is subsumed in the written description requirement (*id*). This means that when the issue of utility is involved, cases decided under the headings "written description," "enablement," "utility," 35 USC § 101, and 35 USC § 112 may be relevant, and certainly cannot be distinguished on the basis of the heading alone.

One of the issues in the *In re Brana* case was whether the applicants proved the claimed compounds useful (*id*, at 1566). That is, whether the tests offered by the applicants to prove utility were inadequate to convince one of ordinary skill in the art that the claimed compounds were useful *as antitumor agents*. The Applicants had pointed to language in the application, and *in vitro* data in the application. The Examiner had pointed to journal articles discussing the therapeutic predictive value of *in vivo* murine tests. The Applicants pointed to a Declaration filed during prosecution with *in vivo* animal data (murine models).

The Court ruled that *the applicants should not have been required to substantiate their presumptively correct disclosure* to avoid a rejection under the first paragraph of § 112, and that the later-filed Declaration was available to prove assertions made in the patent application (*id* at 1567).

The Court specifically addressed the question of whether animal models can be used to demonstrate utility, and commented as follows: "We hold as we do because it is our firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, *even though it may eventually appear that the compound is without value in the treatment in humans*." *id* at 1567. [emphasis added]

Given the clear, direct, and on-point teachings of this case, the next question is whether the applicable law has changed since 1995. The *Brana* case has not been reversed. Indeed, the opinion in the *Brana* case is wholly consistent with the current Examining Guidelines, because both the opinion and the Guidelines cite *In re Marzocchi*, 439 F.2d 220, 223, 169 USP 367, 369 (CCPA 1971) for the same point:

> 2-Burden on the Examiner - MPEP 2164.04 and In re Brana 51 F2d.3d 1560, 1566:
>
> The examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. If an examiner can provide reasons sufficient to create a reasonable doubt as to the accuracy of a particular broad statement put forward by applicant as enabling support for a claim, a rejection under 35 U.S.C. 112, first paragraph can be made. A specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of §112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that sufficient reason for

such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis. Citation omitted.

B. Application of the Applicable Law to the Current Application.

Under the cited law, both the case law and the Examination Guidelines, where a specification disclosure contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented, the disclosure must be taken as in compliance with the enabling requirement of the first paragraph of §112 unless there is reason to doubt the objective truth of the statements contained therein. So, the burden is on the Examiner to show that there is some basis to disbelieve the disclosure with respect to the material described in sub-claims 37-39. Such a rejection can be overcome by pointing to experimental results, which may be *in vitro*, and may be supplied after the file date, provided the new data supports the existing disclosure. In this case, the base claim has admittedly been enabled, and the presently claimed material was disclosed in the application, claimed in the parent patent, and used in an Example in both the parent patent and the present application. This material is enabled by the text of the present application.

C. There is no basis to reject the teachings of this application.

1. The claimed invention is acknowledged to be enabled.

It is the claimed invention that must be examined. The claimed invention is:

A method of transfecting antigen presenting cells, the steps comprising

selecting a gene delivery complex that targets antigen presenting cells, comprising DNA and one or more compounds selected from the group consisting of sugars, polyethylenimine, and polyethylenimine derivatives,

and applying the complex to the skin or mucosa surfaces of an animal,

wherein said DNA comprises a nucleic acid sequence encoding at least one immunogenic protein operatively linked to a promoter. This method is acknowledged to be enabled by the application. The question raised by the Examiner is whether the specification enables the dependent limitations, wherein the protein is from a human immunodeficiency virus (Claim 37); that is replication-defective (38); by virtue of being integration-defective (39).

The Examiner has taken the position that it is insufficient to show that the method induces an immune response (Applicants point out that their burden is to show that the method transfects antigen presenting cells);. that something further, a "statistically significant" "therapeutic or prophylactic effect," that is, "CTL response...adequate to treat or prevent HIV" or "that the *virus* [emphasis added] does not replicate too much and cause disease." Stripped of all the excess verbiage, this is a requirement for either human clinical trials, or enablement of something the applicants have disclosed does not exist.

The USPTO examines an application to determine whether the claimed invention is supported by the text of the application. A single experiment is all that is necessary to establish patentability. Whether a "statistically significant" "therapeutic or prophylactic effect" is in fact present is a matter for the FDA, not the USPTO.

2. The raw materials in question are used in the Experiments

The applicants note that they have pointed out, *supra*, that a replication-defective, integration-defective set of proteins derived from HIV was used in this application to induce an immune response *ex vivo*, to demonstrate the utility of the raw materials being used, that the new method, which is an alternative to the *ex vivo* procedure used in Example 4, was proven up with a marker gene, and that the text of the application at Example 9 discloses that this invention demonstrates that *in vitro* isolation of DC is not required to transfer genes into Langerhans cells, or for gene expression in the lymphoid organs. The raw material described in Claims 37-39 was used in several experiments in the text of the text of this application, and transfected cells *in vitro* and using the *ex vivo* procedure. Use of the raw material is enabled.

3. The Declaration shows a therapeutic result

With respect to the allegations that no evidence that the CTL response is therapeutic or prophylactic in nature, it is noted that the Declaration of Dr. J. Lisziewicz dtd April 27, 2001, filed May 1, 2001 (Evidence Appendix – 3), was filed in the parent patent case and made of record in this case at least as of the date of filing February 21, 2002. This Declaration identifies one of the inventors, a prominent researcher in the field of the invention, discusses the correspondence between the animal model and the course of HIV infection in humans (Background paras 1-3) the similarity of response to drug therapy (para. 4), and the therapeutic benefit of virus-specific T cell mediated immune responses (para. 5). This Declaration further compares the best-available drug treatment (Efficacy, para 1), an enhanced, innovative drug

treatment (Efficacy, para 2), the limits of the innovative drug treatment (para. 3) and the novel immune therapy involving the use of a complex of PEI-mannose and plasmid DNA encoding an integrase-defective SHIV in sugar-water solution (paras. 4 and 5). The animals' response to treatment is discussed in detail (Efficacy, paras. 6-10), and summarized as showing increased CTL response associated with control of virus replication and improved survival time (Efficacy, paras. 11 and 12). The inventor states that the result, control of virus replication after the interruption of drug treatment during chronic infection or AIDS, is new. (Id.)

4. Peer-reviewed articles show a therapeutic result

Further, the cited publications by the inventors confirm the statements that are already in the application. For example, the application discloses that CTL responses are associated with therapeutic effects at page 4, lines 7-11: "Expression of foreign genes in antigen presenting cells (APC) may be used to generate efficient CTL response in animals. Therefore, gene transfer and genetic modification of APC has the potential to generate effective vaccine and therapeutic approaches ...." That is, the application discloses that generation of a CTL response is a legitimate marker for a therapeutic effect, and the peer-reviewed journal articles confirm that others agree with the inventors on this point.

See, for example, Lisziewicz, et al., "DermaVir: A Novel Topical Vaccine for HIV/Aids" J Invest Dermatol, 2004 detailing the use of the presently claimed invention to produce CTL responses; (Evidence Appendix – 4)

Lisziewicz, et al., "Control of Viral Rebound through therapeutic immunization with DermaVir", AIDS 2005, 19:35-43 which discloses studies showing low toxicity, enhanced viral control, and enhanced longevity; (Evidence Appendix – 5) and

Lisziewicz, et al., "Induction of Potent Human Immunodeficiency Virus Type 1-Specific T-Cell-Restricted Immunity by Genetically Modified Dendritic Cells J Virol. Aug 2001, p. 7621-7628, (Evidence Appendix – 6) where the Examiner's technical questions about the differences between a replication-defective retroviral particle and plasmid DNA encoding the same are addressed. Expression of viral antigen by plasmid DNA is compared to that of the replication-defective control in primay human lymphocytes, macrophages, and dendritic cells in Fig. 1 b-d.

5. Where the Applicants have experimental results, the state of the art is irrelevant

The Examiner's comments about the state of the art at the time the application was filed are true to the extent that the field was unpredictable; however, it does not follow that this application must set forth whatever any prior art references predicted to be needed. This application sets forth the details of basic research into the physiological mechanisms of raising a CTL response, and discloses important and useful advances in new materials, a theoretical and practical basis for targeting antigen presenting cells, and a method of vaccination that does not require injection. It is not at all surprising that the disclosure of this application does not conform to that of the predictions in the prior art. The standard for invention is that the subject matter is new, useful, and non-obvious. If the present invention were merely in the ambit of the prior art predictions, it would be properly rejected for being either not new, or obvious over the references currently cited.

The Examiner's comment that "it was also unknown how to make a retrovirus (changed in this rejection to "HIV vector") with the adequate amount of replication that would provide an adequate cellular immune response without causing disease" is disingenuous. The Examiner has continually refused to recognize the experimental evidence distinguishing between a "replication-defective retrovirus" and a "DNA encoding a replication-defective retrovirus." Mere substitution of a language change in this rejection does not make it valid. The present invention does not use a retrovirus with a finely-tuned reproductive capacity. In brief, a plasmid DNA encoding a replication defective, integrase-defective HIV is not the same thing as the corresponding viral particle, and the difference in the materials has been exploited by the inventors.

The Examiner's discussion of the experimental support offered by the Applicants does not consider the teachings of the application or the experiments as a whole. The *in vitro* data complements the *in vivo* data. The experimental support in the application must be taken as a whole, for what each experiment provides. The publications are cited to confirm the statements in the text of the application, and were never suggested to be separate, enabling disclosures.

The Examiner's criticism that the subsequent publications by the inventors contain experiments under a variety of conditions is inapt. For example , the Examiner makes much of the use of a tradename, DermaVir, in 2005 article that cited another article, Lisziewicz, et al., "Induction of Potent Human Immunodeficiency Virus Tye 1-Specific T-Cell-Restricted

Immunity by Genetically Modified Dendritic Cells" J Virol.(2001) pp 7621-7628. However, the referenced 2001 article discloses the construction of plasmid DNA encoding the replication-and integration-defective pLW/int- as the raw material in terms that clearly are acceptable to those of ordinary skill in the art. This is the material used in Example 1, page 18, line 31.

The Examiner's statement that the article by the inventors, Lori, et al., "Cellular Immunity and DNA vaccines for the treatment of HIV/AIDS Curr. Me. Chem. - Anti-Infective Agents, 3 (2004) pp 31-41 (Evidence Appendix 7), somehow renders the invention disclosed in this application unenabled because that article reports the failure of the first phase III HIV preventive vaccine trial (AIDSVAX B/B) is incorrect as a matter of law and as a matter of fact.

This kind of rejection has been considered, and found to be unacceptable. "We hold as we do because it is our firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment in humans." *In re Brana* at 1567, quoting *in re Krimmel* 292 F2d 953, 130 USPQ at 219.

In addition, the failure of that vaccine trial merely confirms the inventors' own disclosure of the need for other materials. AIDSVAX B/B is a preventive vaccine designed to produce an antibody response (Evidence Appendix 7, col. 1, 2nd para.)

That trial demonstrates failure of others, and the result was predicted in another application by the present inventors, 08/803,404 (Evidence Appendix – 2), at page 3, first paragraph where vaccines directed to the production of an antibody response were disclosed to be problematic for HIV. The present inventors, in that application, proposed raising a different kind of immune response, using a different kind of material, that is, a method for raising a cellular immune response in a mammal, the steps comprising transducing antigen presenting cells selected from the group consisting of Langerhans cells, dendritic cells and mixtures thereof, with a plasmid DNA construct that encodes a replication-defective retrovirus, and exposing a mammalian host to the cells in a manner that allows the cells to express the construct in the lymphoid organs of the host, whereby a cellular immune response to the retrovirus is raised by the host. This is an alternative approach offered at a time when it was much needed, as confirmed by the Ready reference cited by the Examiner.

The Lori (2004) (Evidence Appendix – 7) article does discuss the present invention: "our DC targeted HIV vaccine, DermaVir, a topical, therapeutic vaccine that has demonstrated immunological and clinical benefits in rhesus macaques" at page 32, Column 1, 1st full para, lines 1-5 *up*. The article presents pre-clinical studies, page 38-39, a theoretical basis to explain why the vaccine differs from other vaccines (page 39, 2nd full para) and a suggestion for its treatment as a new antiretroviral approach complementary to that of various drug classes (page 39, paragraph bridging Cols 1 and 2). This is by no means an indication that the material has no therapeutic value.

D. Conclusion – This Enablement Rejection must be withdrawn

The Examiner's requirement to show an effect beyond that of the claimed invention is legal error. The Examiner's alternative requirement that, in order for the presently claimed invention to be enabled, the text of the specification must show anything other than how one of skill in the art can make and use the claimed invention, that is, to include any number of items that those in the prior art or analogous art may have predicted would be needed, is also legal error. The Applicants have properly stated the applicable law, which does indeed relate to the current rejection for alleged lack of enablement.

The Applicants recognize the difference between the Examiner and the USPTO, and think that responsibility for attempts to evade the settled law of the Federal Circuit rests with the USPTO, not the Examiner. Further, the applicants have a right to a clear and candid statement of the examination policy of the USPTO, which should be applicable to all art groups. If the USPTO has a policy try yet again to push for a ruling that clinical results will be required for medical inventions, or that prior art references can be used to determine the content of an application's disclosure, or that subsequent publications can "unenable" the disclosure in a patent application, then the applicants have a right to know this and have the policy opened up to public debate. The Applicants have reviewed the status of the applicable law relating to any requirement for data showing a "therapeutic or prophylactic effect" or in the alternative, a laundry list of requirements pulled from prior art documents, or any use of subsequent publications to "unenable" a disclosure, and cannot find them in the case law, MPEP, or Examiner's training materials.

The Applicants point out that they have, as a result of some sort of acknowledged but undefined policy of the USPTO, have been subjected to extraordinary expense, delay in

prosecution, and loss of term for their patent applications, based on the field of interest rather than the merits of the case. Accordingly, an extension of patent term equal to the entire span of prosecution of this application is requested.

4. Indefiniteness – Claims 23-26, 28, 30-33, 35, 37- 43

The Applicants have a right to uniform application of the patentability standard (MPEP 706). Piecemeal Examination is to be avoided (MPEP 707.07(g)). Certain technical objections, (e.g., negative limitations, indefiniteness) should not be made where the examiner, recognizing the limitations of the English language, is not aware of an improved mode of definition. (MPEP 707.07(g)). Inventions relating to HIV/AIDS and cancer are specifically important, and suitable for expedited processing. (MPEP 708.02 X.) And, applications that are substantially allowable should be considered special and prompt action taken to require correction of formal matters (MPEP 1301). Even in ordinary cases, the Examiner should never overlook the importance of his or her role in allowing claims which properly define the invention (MPEP 706). The examiner's action should be constructive in nature and when possible should offer a definite suggestion for correction (MPEP 706 II).

The Applicants submitted a set of Claims that could have been allowed on the first office action in this case. The Applicants have, in good faith, used the text of the parent application's claims, and consulted with the Examiner to draft the present claims. Despite their own clear right to act as their own lexicographers, the Applicants have abandoned their original language in an effort to conform the claims to their invention to that favored by the Examiner, and repeatedly amended the claims for that purpose. The Applicants have pointed to support in the application and also asked, in writing, for a definite suggestion, as is their right under MPEP 706, and the Examiner has not responded. It is noted that the Examiner has failed to proffer acceptable language and failed to recognize the distinction between an "argument" and a statement regarding the scope of the claims that will necessarily give rise to an estoppel, should the patent ever be subject to challenge. It is noted that the Applicants have in the past attempted to amend Claims in response to the present Examiner's criticisms, to no good result.

Accordingly, the Applicants respectfully request that, pursuant to MPEP 707(g), the present rejections be withdrawn because the Examiner has impliedly admitted that he is not aware of an improved mode of definition. With respect to the specific objections, the applicants note:

Claim 23 – Nexus

Claim 23 was filed as "A method of transducing antigen presenting cells of the skin" and was amended in response to various formal objections by the Examiner. Now it is said to show no "nexus" between the preamble, "a method of transfecting antigen presenting cells" and the body of the claim where the complex is applied to the skin. The present objection would presumably call for addition of a "whereby" clause. If such an amendment will resolve this issue without raising others, the applicants are will to make it.

Claim 23 – transfection

Claim 23 is said to be indefinite for use of the word "transfection," which is defined on page 6, lines 12. The applicants amended the claims to use this word instead of "transduction" because that word was considered indefinite as being too easily confused with "infecting."

Claim 23 – applying

Claim 23 is said to be indefinite because the term "applying" could be construed as "injecting." The applicant cited the ordinary dictionary definition of the words and stated that the two are distinct at least as far back as June 7, 2004.

Claim 23 – "gene delivery complex that targets antigen presenting cells"

This phrase is supported in the application at the section titled "Target Cells" and most specifically at page 12, lines 25-27: "If the gene delivery complex is made with IgG or a polyethylenimine modified with an appropriate starch or sugar, it will be taken up mainly by antigen presenting cells."

Claim 30 – narrowing limitation not applicable to all materials in independent claim.

Claim 30 has the phrase "method of claim 28, wherein the complex comprises a 5:1 ratio of polyethylenimine derivative nitrogen per DNA phosphate" remains unclear, and the Examiner's comments would suggest Claim 30 should also limit the complex to having polyethylenimine or a polyethylenimine derivative; such an amendment would be acceptable to the applicants, provided it would resolve the issue without raising others.

Claim 31 – "is formulated in a glucose solution"

The applicants have pointed out at least since June 7, 2004 that their experimental results in this application show that, as a practical matter, the complex may be formulated in a sugar solution in at least two ways, namely by forming the PEI-DNA or PEI-mannoseDNA complex and adding a glucose solution (Example 8), or placing DNA in a glucose solution (Example 10).

As a result, it does not matter whether the glucose solution is a solution in which the complex of claim 23 is put in or encompasses a complex made up of PEI conjugated with glucose, because both have been shown to work, and are within the scope of the invention. If the claim can be clarified by substituting "sugar" for – glucose –, the applicants can agree to such an amendment.

5. Anticipation – Claims 23-26, 28, 30-32, 37, 40, 41 and 43

Claims 23-26, 28, 30-32, 35, 37, 40 41 and 43 remain rejected under 35 U.S.C. 102(e) as being anticipated by Behr (US Patent 6,013,240, Jan. 11, 2000; 102(e) date=2-28-97) as supported by Carson (US Patent 5,679,647)

Behr is said to have inherently taught the present invention because a plasmid DNA encoding a marker gene, Luciferase, was complexed with PEI in a sugar solution and said to transfect brain cells. Carson is said to support the inherency argument by teaching a gene delivery complex applied to the skin transfects dendritic cells. The phrase "transfecting antigen presenting cells" in the preamble has not been deemed to have patentable weight.

Claims 25, 26 and 43 are said to be included because they are not limited to a compound that is mannosylated PEI or PEI "from a PEI 22 kDA;" claims 25, 26 and 43 are said to encompass non-sugar-modified PEI solubilized in glucose as in parent claim 24.

Claims 28 and 30 are said to be included because Behr taught that between 5-20 equivalents of PEI amines are used relative to one DNA phosphate (col. 8, lines 15-19). The instant specification teaches that the ratio of 5:1 cause the complex to be electrostatically neutral (¶ bridging pg 21-22).

Claims 35 and 41 are said to be included because administering the complex to the skin/mucosa as taught by Behr inherently would act activate APCs by toxin activation. Cells would start expressing luciferase and this firefly "toxin" would be recognized as foreign by the animal, thereby activating APCs, including Langerhans cells.

Response – Anticipation – Claims 23-26, 28, 30-32, 37, 40, 41 and 43

The Applicants have a right to uniform application of the patentability standard (MPEP 706). The Applicants have requested a written statement by the USPTO stating the legal basis for failing to withdraw a 35 USC §102 rejection where the limitations are not found within a single reference, and for maintaining an inherency argument where no evidence exists that the supposed results (immune response to luciferase) have been obtained. No such response has been forthcoming.

A. Applicable Law – 35 USC 102

The Applicants note that the latest set of Examiner's Guidelines was modified in with respect to 102(e)(2), not relevant here, in 2000.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. The **identical** invention must be **shown in as complete detail as is contained in the ... claim.** (emphasis added) The elements must be arranged as required by the claim. MPEP 2131. Multiple references may be used to (a) prove that a reference was an enabling disclosure, (b) explain the meaning of a term, or (c) show that a characteristic not disclosed in the reference is inherent (MPEP 2131.01). The burden is on the Examiner to first show that the claimed composition or machine is disclosed **identically** (emphasis added) by the reference, if an additional reference is to be used to show enablement (MPEP 2131.01 I.).

The discovery of a new use for an old structure based on unknown properties of the structure might be patentable to the discoverer as a process of using. (MPEP 2112.02)

Extrinsic evidence may be used to establish that a reference inherently discloses an invention. To do this, the extrinsic evidence "must make clear that the missing descriptive matter is *necessarily* present in the thing described in the reference [emphasis added], and that it would be so recognized by persons of ordinary skill." "Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient." (citations omitted) *In re Roberts*, 169 F.3d 743, 49 USPQ2d 1949 (1999). "We do not see how a disclosure or combination of disclosures leaving one to rely on fortune in choosing the referred to material can function as anticipation. Absent a showing of some reasonable certainty of inherency, the rejection under 35 USC 102 must fall." *In re Brink*, 419 F.2d 914, 918, 164 USPQ 247 (1970).

B. Factual Background: The Scope and Content of the Prior Art, the Present Invention and the Differences between the Claimed Invention and the Prior Art

The Behr Reference (Evidence Appendix – 12)

The Behr reference relates to the use of PEI as an adjuvant for gene therapy, preferably in conjunction with plasmid DNA, although a wide variety of other materials are disclosed as well.

Gene therapy is disclosed to consist in correcting a deficiency or an abnormality (mutation, aberrant expression, and the like) or in effecting the expression of a protein of therapeutic value by introducing genetic information into the affected cell or organ (Col. 1, lines 11-15). Gene therapy is a field distinct from immunotherapy, and this reference discloses that immunogenicity, that is, the result obtained by the inventors, is to be avoided in this context (Col. 1, line 51).

The reference states that PEI can be used in a wide variety of cells, (tumor cells, liver cells, haematopoietic cells Col. 5, lines 41-43), in a wide variety of configurations, including using a wide variety of targeting elements (sugars, peptides, oliconucleotides, or lipids Col. 5, lines 55-57; sugars are listed as useful for targeting the asialoglycoprotein receptors at Col 5, lines 64-65), for a wide variety of purposes (for example, the production of therapeutic products including enzymes, blood derivatives, hormones, lymphokines,...growth factors, neurotransmitters...synthetic enzymes, etc,, -- a list that includes thousands of items. See Col. 3, lines 29-44. Antigenic peptides are also listed at Col. 3, line 57-67, as well as antisense genes (Col. 3, line 45), sequences (Col. 4, line 1, and upstream signals to control therapeutic genes (Col. 4, lines 25-29) and that it can be used in formulations with a view to topic, cutaneous, oral, rectal, vaginal, parenteral, intranasal, intravenous, intramuscular, subcutaneous, intraocular, transdermal, and the like (Col. 6, lines 1-4) in formulations that that might be isotonic sterile solutions, dry, water or saline (Col. 6, lines 9-12 as appropriate *to enable injectable solutions to be formed* (line 13, emphasis added). Both direct injection and topical administration are said to be preferred (Col. 6, lines 5-9), but only direct injection is shown in any experiments, and there is no disclosure of how to accomplish gene delivery by means of topical administration.

Claim Limitations Missing from the Behr reference

Among the differences between this reference and the presently claimed invention are that the reference does not disclose the transfection of antigen presenting cells, or the targeting of antigen presenting cells, a most significant subset of cells, and prominent by its omission, or formulations that can be used for needleless, *in vivo* delivery of genes into any cells, much less antigen presenting cells, or any *in vivo* method of delivery except injection.

Similarly, the reference does not disclose that glucose and PEI derivatives could be used in the claimed method (Claim 24) or that the PEI derivatives can target the mannose receptor instead of the asialoglycoprotein receptors (Claim 25), or anything about mannosylated